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The objective was 1) to quantify the metabolic responses of skeletal muscle to a fixed exercise load, 2) to identify alterations in the response of muscle to exercise after physical conditioning, and 3) to quantify leucine flux (influx and efflux) across cell membranes of resting muscle.

To identify the metabolic alterations accompanying muscular hypertrophy, we have measured net exchange of glucose, lactate, oxygen, and amino acids in ten healthy nontrained and six weight trained young male volunteers before, during, and after sixty minutes of hand ergometer exercise (7.5 kilopond·meters·minutes^{-1}). The forearm muscle conditioning program increased arm volume by 7% and wrist curl strength by 55%. The major metabolic differences between untrained and trained men appeared during exercise. The increase in glucose uptake and lactate release were significantly greater in untrained subjects. On the other hand, the increase in alanine release was greater in trained subjects. This suggests that less tissue hypoxia developed at the same moderate work load in hypertrophied muscle. With the acceleration of glycolysis that accompanies exercise, hypertrophied muscle is able to direct more pyruvate toward alanine synthesis and away from lactate production. Leucine flux into muscle at rest in nontrained subjects was +198 ±54 nmoles/minute/100 ml forearm (fractional extraction of leucine from arterial blood was 27%), and efflux was -225 ±74 nmoles/minute/100 ml forearm. Of the influxing leucine, 2% was immediately oxidized.

Energy and Nitrogen Metabolism of Peripheral Tissues in Intact Man

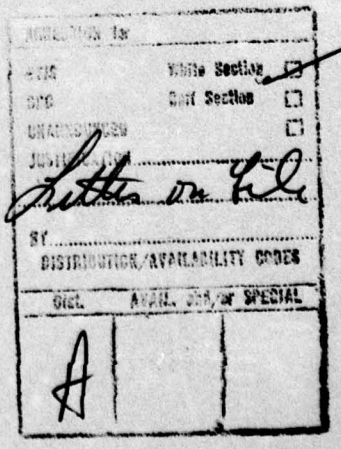
FINAL REPORT

Principal Investigator: Thomas Pozefsky, M.D.

Contract: N-00014-67-A-0163-0015

Work Unit Number: NR 101-896

(From the Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205)



Work under the contract was begun May 1, 1972 and terminated November 30, 1974, when the Principal Investigator resigned his full time position at the Johns Hopkins University School of Medicine to enter part time private practice of medicine.

The objective of the studies was: 1) to quantify the metabolic responses of skeletal muscle to a fixed exercise load, 2) to identify alterations in the response of muscle to exercise after physical conditioning, and 3) to quantify amino acid influx and efflux across muscle cell membranes. The forearm technique was utilized as described by Andres, R. et al (J. Clin. Invest. 35:671, 1956), and modified for flux studies by the application of isotopic techniques. Although Dr. K. L. Zierler was initially a Co-Principal Investigator, his July 1972 departure from the Johns Hopkins University terminated his relationship with the project. Dr. Pozefsky was joined at that time by Dr. R. T. Moxley, a Research Fellow in Medicine, who collaborated in all studies. Dr. Moxley currently is Assistant Professor of Neurology at the University of Rochester School of Medicine.

Certain technical problems were addressed in the first year of funding. First, a rapid and reproducible spectrophotometric method for measuring the oxygen content of blood was adapted from that of Nahas, G. G., et al (Science 113:723, 1951). Second, because studies were to emphasize the metabolism of amino acids, and because the then recent studies of Elwyn, D. H. et al (Am. J. Physiol. 222:1333, 1972) suggested a role for erythrocytes in the interorgan transport of amino acids, it became necessary to determine whether whole blood rather than plasma was the biologic fluid of choice for measurement of amino acid concentrations. Plasma had been traditionally used in studies of forearm muscle amino acid metabolism. We elected to use whole blood because significant differences were noted in the calculated values for muscle balance depending on the fluid utilized. These differences were, however, numerically small. Third, it was necessary to construct a hand ergometer with which a precisely quantified hand grip exercise load could be imposed. With this ergometer a moderate exercise load was selected that could be sustained by our experimental subjects for one hour (7.5 kilopond$\cdot$meters$\cdot$minutes^{-1}). Fourth, a method was selected to induce conditioning and hypertrophy of forearm muscles. The technique of DeLorme, T. and A. C. Watkins (Arch. Phys. Med. 29:263, 1948) was utilized involving daily repetitive wrist curls and reverse wrist curls over a period of ten weeks. Finally, our Amino Acid Analyzer was modified for stream-splitting and fraction collecting to measure amino acid specific activity.

Human studies were begun in mid-1973 and continued through November 1974. Ten normal young male volunteers were studied during a sixty minute preexercise control period, a sixty minute period of hand grip exercise, and a postexercise recovery period. Six subjects underwent the ten week period of forearm muscle conditioning, and identical studies were then performed. In addition, four nonconditioned subjects received infusions of ^{14}C-leucine lasting eighty minutes while forearm tissues were at rest to quantify leucine influx and efflux across forearm muscles as well as leucine oxidation. Thus, during the contract period a total of twenty successful studies were performed.

Characteristics of the exercised subjects studied are given in Table I. There were twelve subjects studied before conditioning, four of whom were re-studied after conditioning. Two subjects undergoing forearm studies were studied after conditioning only. The results may be summarized as follows. Forearm conditioning increased maximum wrist curl strength by 55% (Table II). This is evidence for conditioning. Forearm volume increased 7%. This is evidence for hypertrophy. The exercise induced increase in forearm blood flow and oxygen consumption was the same in untrained and trained subjects (Figures 1 and 2). The exercise induced increase in glucose uptake and lactate release were greater in untrained subjects ($P < 0.05$ for each, Figure 2). On the other hand, the increment in alanine release was greater in trained subjects ($P < 0.025$, Figure 2). This suggests that less tissue hypoxia developed at the same moderate work load in hypertrophied muscle since greater alanine release and lower lactate output occur during exercise in weight-trained men. With the acceleration of glycolysis that accompanies exercise, hypertrophied muscle is able to direct more pyruvate toward alanine synthesis and away from lactate production. The increase in alanine output occurred despite lower glucose uptake in exercise by weight-trained men, suggesting a greater role for free fatty acids as an energy source in hypertrophied muscle. While exercise induced an uptake of branched chain amino acids in both groups, no difference between the two groups was observed. Exercise did not alter the transport of other acidic and neutral amino acids. In leucine flux studies (nonconditioned muscle at rest) leucine influx was +198 $\pm$54 nmoles/minute/100 ml forearm (the fractional extraction of arterial leucine was 27%), and efflux was-225 $\pm$74 nmoles/minute/100 ml forearm. Of the influxing leucine, approximately 2% was immediately oxidized.

A technical description of the differences between using whole blood and plasma for the determination of amino acid balance across forearm muscle has been published (see reference 1 below), and an abstract describing the findings in untrained and trained subjects has been published (see reference 2 below). Dr. Moxley is preparing a definitive paper describing the effects of training on the metabolic response of muscle to exercise.

BIBLIOGRAPHY:

1) Pozefsky, T., R. G. Tancredi, R. T. Moxley, J. Dupre, and J. D. Tobin. Effects of brief starvation on muscle amino acid metabolism in nonobese man. J. Clin. Invest. 57:444, 1976.

2) Moxley, R. T., and T. Pozefsky. Metabolic changes accompanying skeletal muscle hypertrophy. Clin. Res. 24:366, 1976.

Thomas Pozefsky, MD

TABLE I Subject Data: Age, Height, Weight

Subject	Age years	Height inches	Weight pounds
A.D.	21	71	183
J.T.	21	70	188
S.K.	22	73	177
R.L.	22	71	173
G.D.	22	76	201
P.A.	25	69	160
M.O.	25	71	152
E.H.	25	68	170
D.T.	26	69	143
D.C.	27	70	173
R.S.	27	71	188
R.C.	27	71	157

TABLE II. Serial Changes in Wrist Curl Strength and Arm Volume During Weight Training*

	Maximum Weight with One Wrist Curl			Arm Volume		
	Time after start of training			Time after start of training		
	0	10 weeks	% increase	0	10 weeks	% increase
A.D.	131	170	30%	1990	2120	7%
S.K.	85	186	120%	1785	2010	13%
G.D.	166	203	22%	1948	1998	3%
D.T.	91	156	75%	1420	1520	7%
D.C.	155	198	27%	1755	1783	2%
R.C.	82	130	58%	1313	1425	9%

* Modification of DeLorme Method: DeLorme, T., and A.C.Watkins. 1948. Techniques of progressive resistance exercise. Arch. Phys. Med. 29: 263-273.

Arm volume was determined by water displacement and measured the volume of arm from a line drawn between the upper borders of the humeral epicondyles distally.

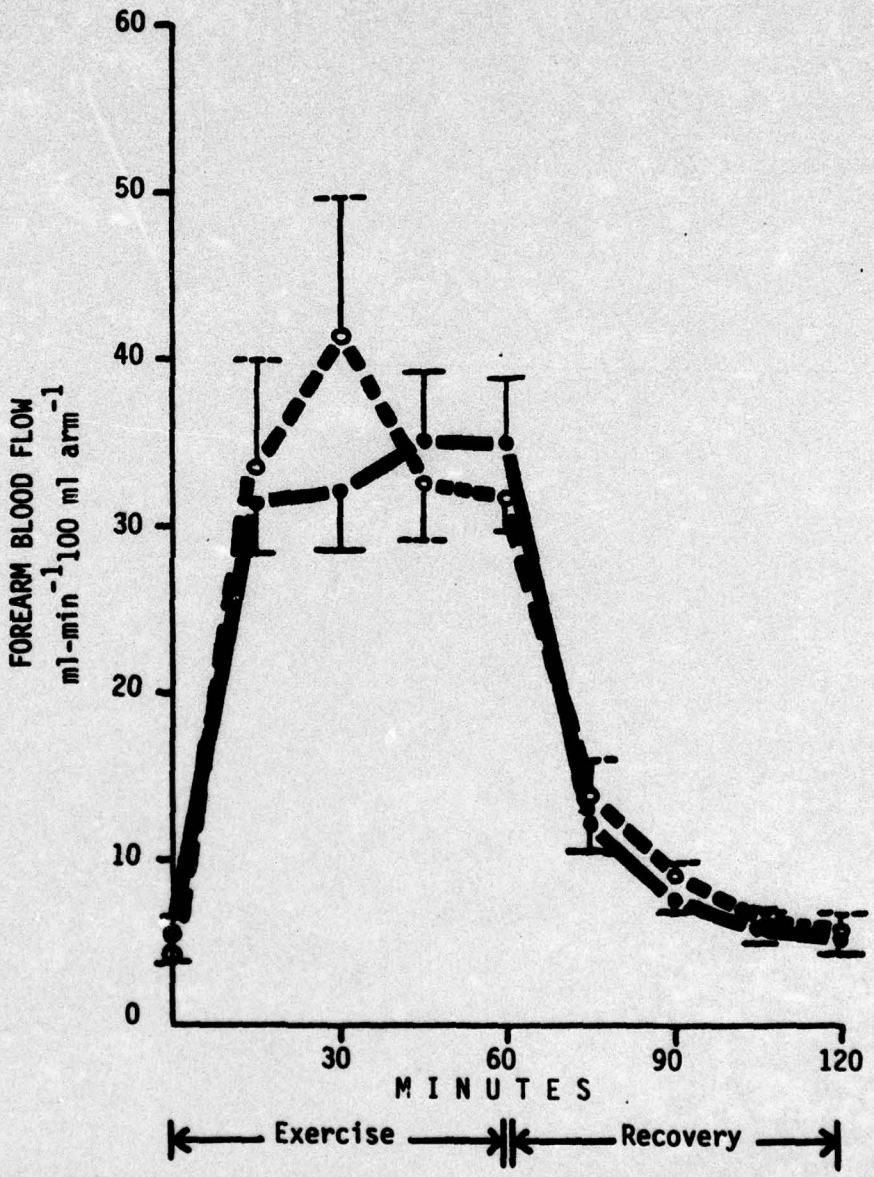


Figure I. Effect of hand grip exercise on ipsilateral brachial arterial blood flow in 10 untrained (●—●) and 6 trained (○···○) subjects. Mean ± SEM values have been plotted.

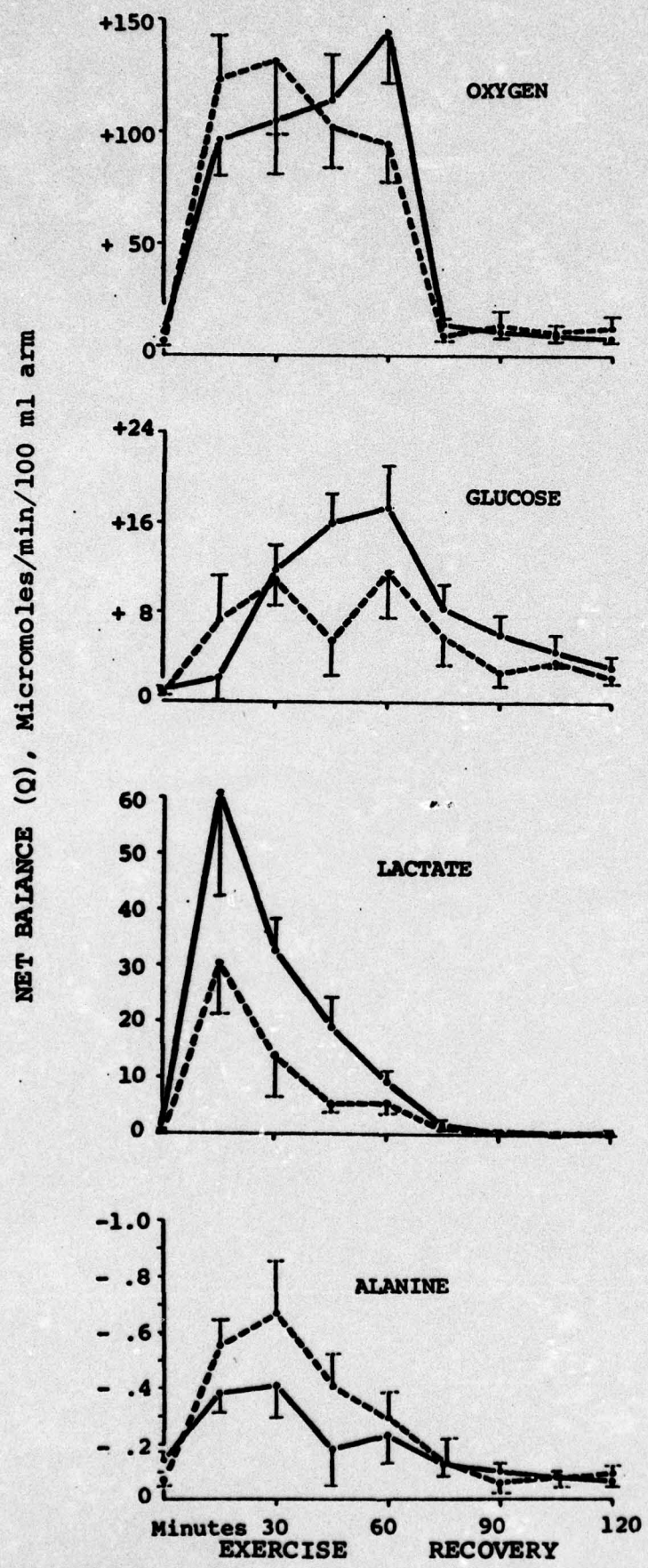


Figure 2. Effect of hand grip exercise on muscle balance (Ω) of oxygen, (glucose, lactate and alanine in 10 untrained and 6 trained subjects. Mean ± SEM values are plotted.